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Title: A Fragment Library for Drug Activity in Gram Negative Bacteria

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A Fragment Library for Drug Activity in Gram Negative Bacteria

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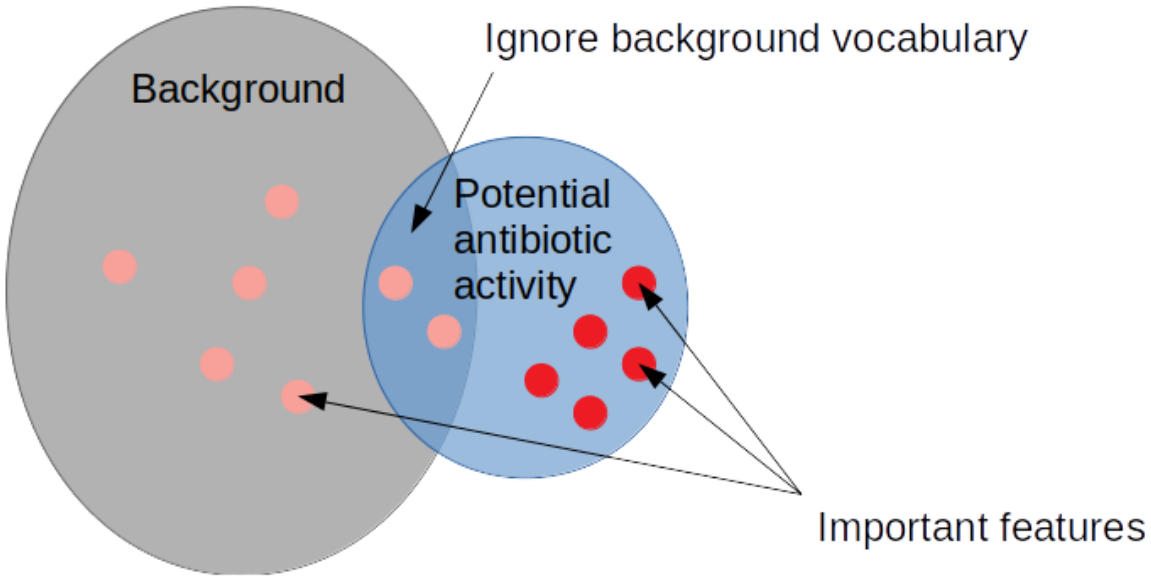
December 20, 2018

"*k*-spectrum" Analysis



- Idea: Find a "vocabulary" of antibiotic resistance
- How? Apply *tf-idf* to molecular fragments of various radii
- Similar to an approach for identifying peptide fragments important for antimicrobial action [5]

[5] Cipcigan, Flaviu, et al. "Accelerating molecular discovery through data and physical sciences: Applications to peptide-membrane interactions." The Journal of Chemical Physics 148.24 (2018): 241744.

k-spectrum Workflow

- Separate dataset into "hits" and background based on metric (eg MIC)
- Compute all k-mers in each molecule, defining k-mer as atoms within radius k of each atom in molecule
- Compute $T_i = tf\text{-}idf_i$ of a k-mer k_i in a set where

$$T_i = \sum_j^{|M|} \frac{n_{i,j}}{|m_j|} \times \log\left(\frac{|M|}{|d : k_i \in d|}\right) \tag{1}$$

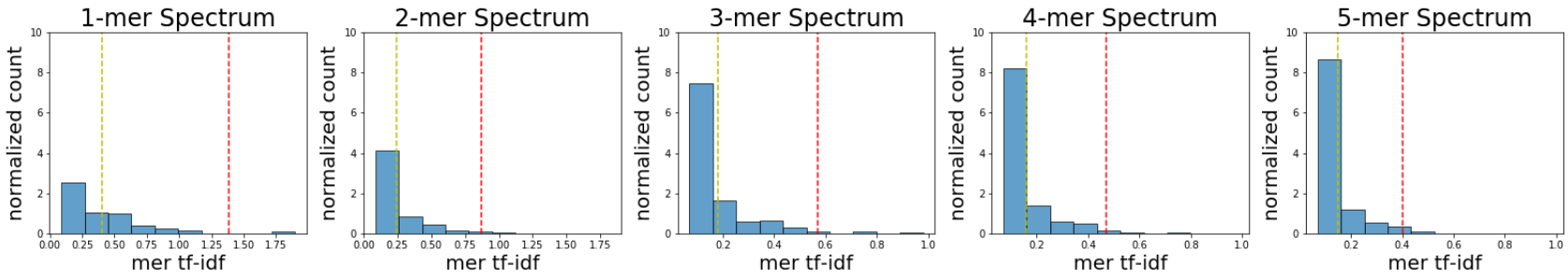
- $|M|$ is the number of molecules in the set, $|m_j|$ is the number of atoms in the jth molecule, $n_{i,j}$ is the number of times k_i is found in m_j, and $|d : k_i \in d|$ is the number of molecules containing k_i
- Choose all molecules beyond $\mu + 3\sigma$ in hits but not background to be "hot" (very important)

Notes on Fragments

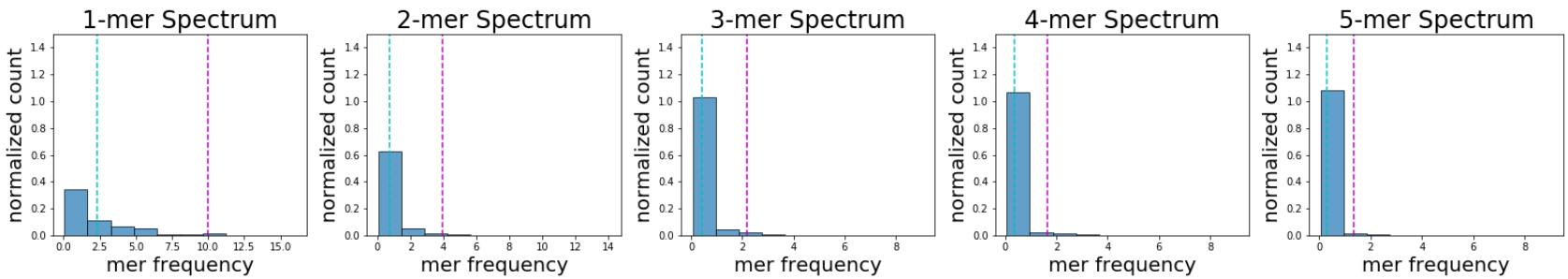
- These are environments of different radii around a central atom
- We are not considering which atom is the central atom, however
- But a ring with one bond off the side is a lonely ring, not just any ring
- Really need to think in terms of neighborhoods, not exactly fragments, which makes them a bit harder to search for...
- We are adjusting for seeing rings from multiple central atoms though

k-spectra for different mutants based on MIC

Wild Type Hits



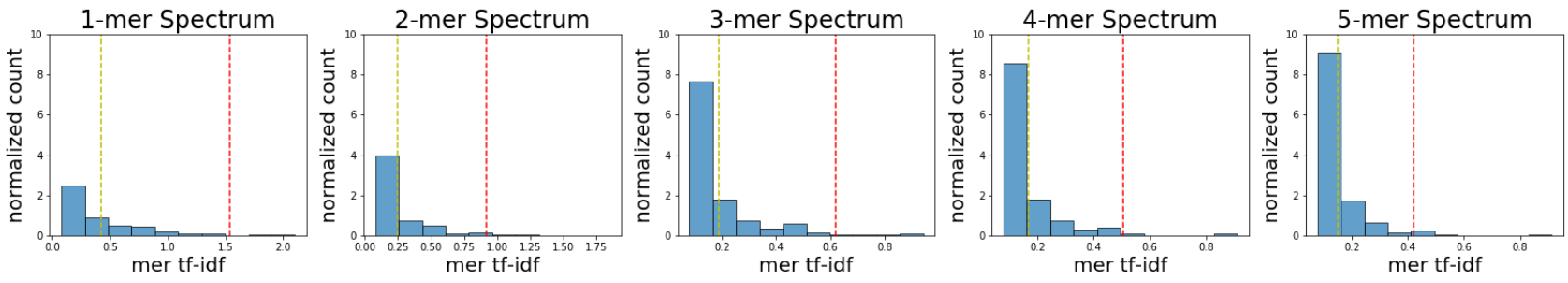
Wild Type BG



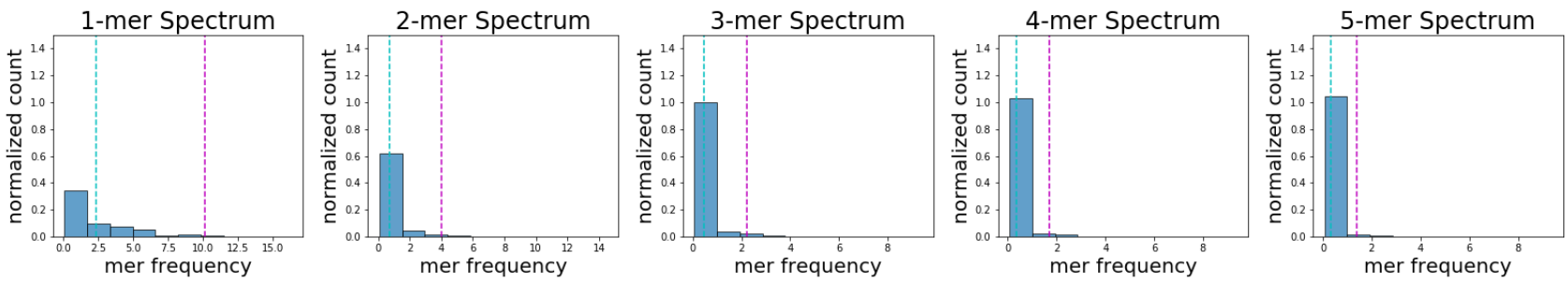
- Used lowest 10% MIC for hits in all columns

k-spectra for different mutants based on MIC

PΔ Type Hits

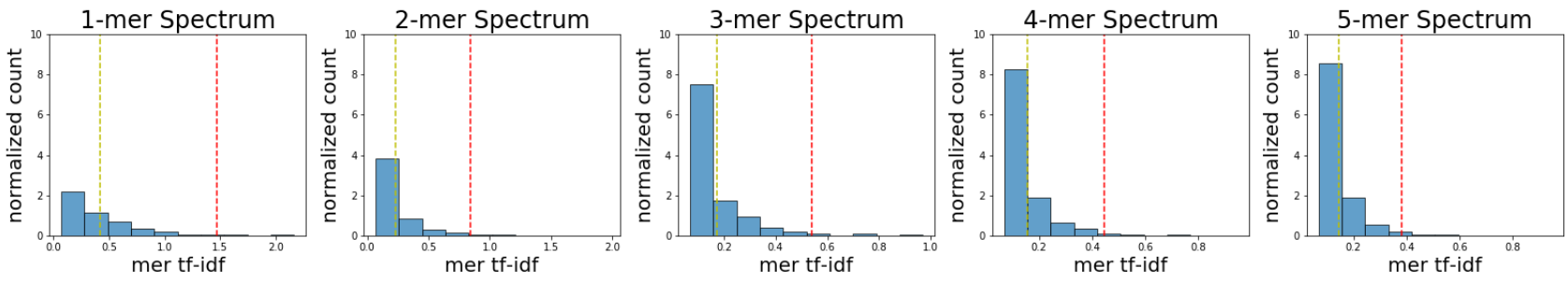


PΔ6 Type BG

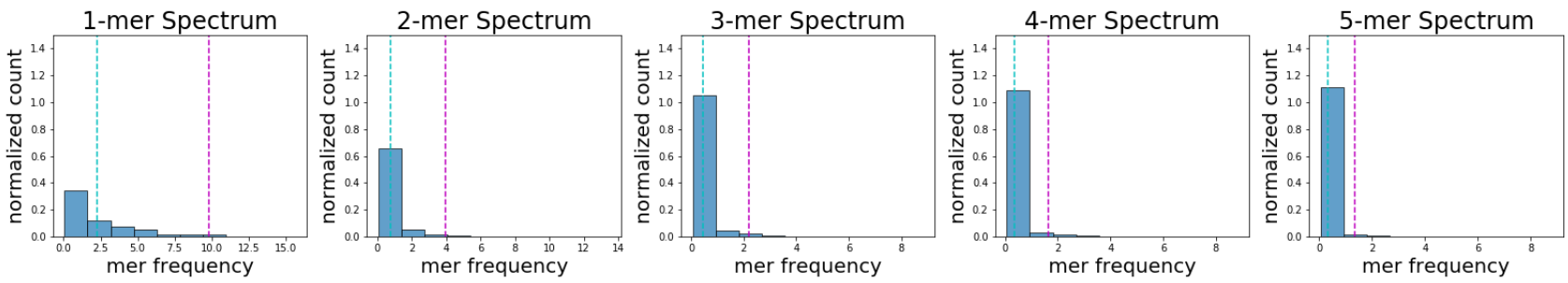


k-spectra for different mutants based on MIC

Pore Type Hits

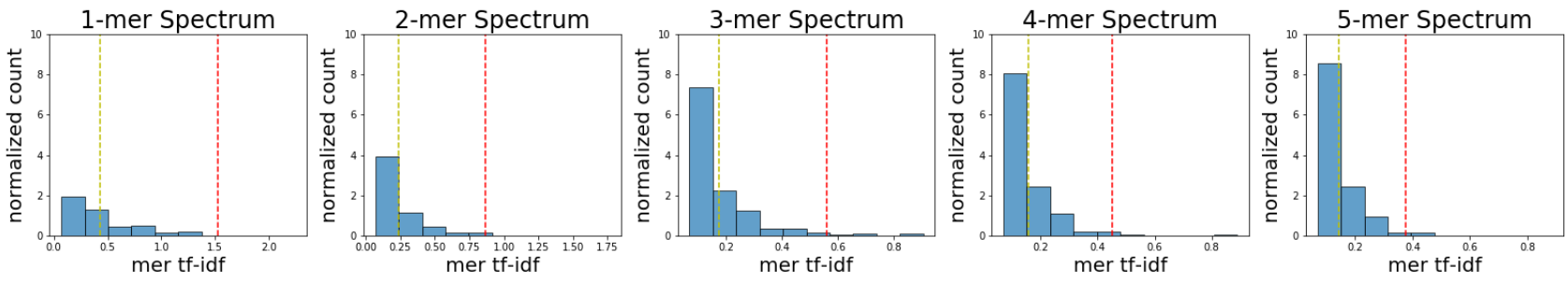


Pore Type BG

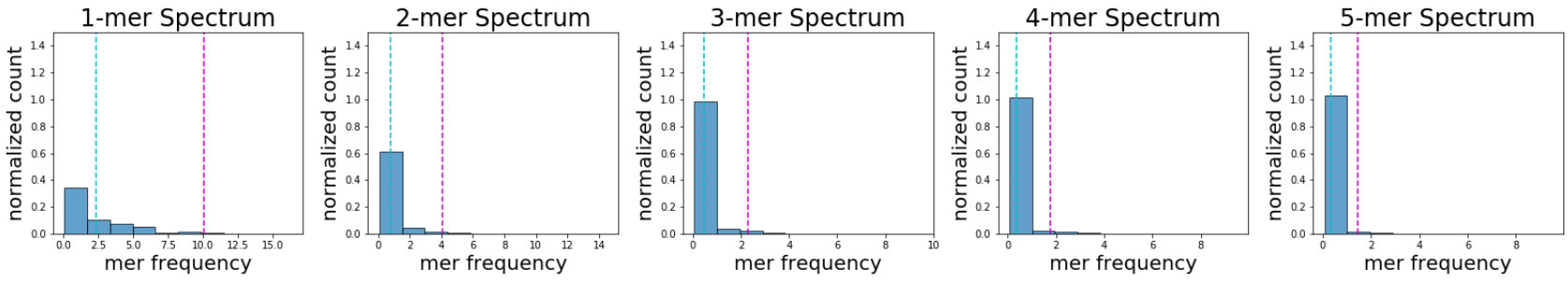


k-spectra for different mutants based on MIC

PΔ6-Pore Type Hits

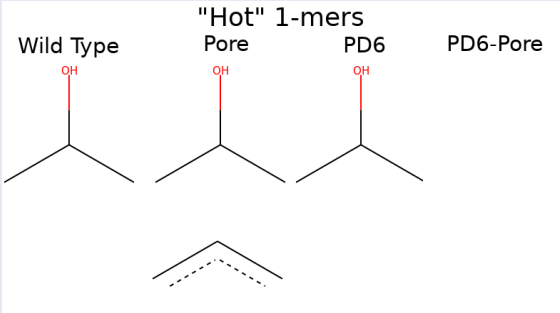


PΔ-Pore Type BG

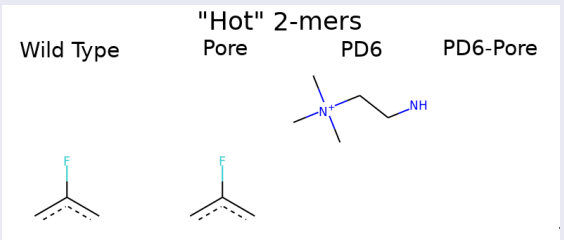


Important *k*-mer molecular fragments from MICs

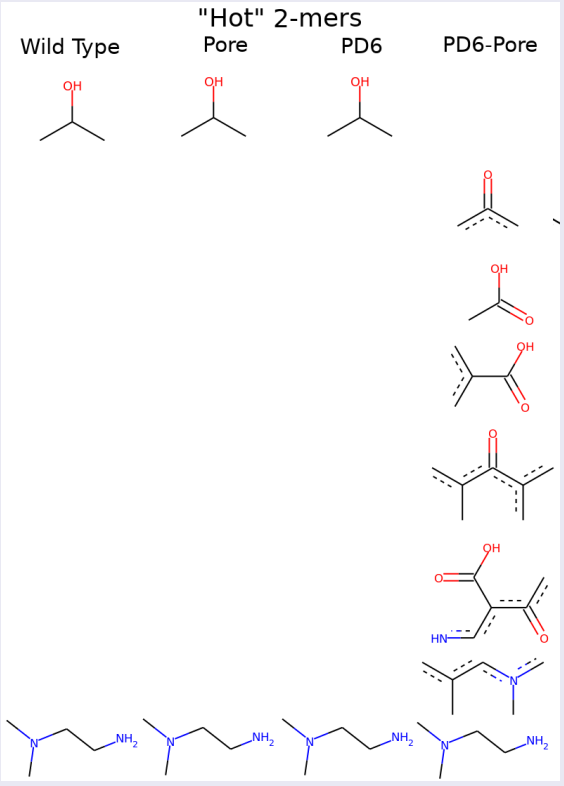
1-mers



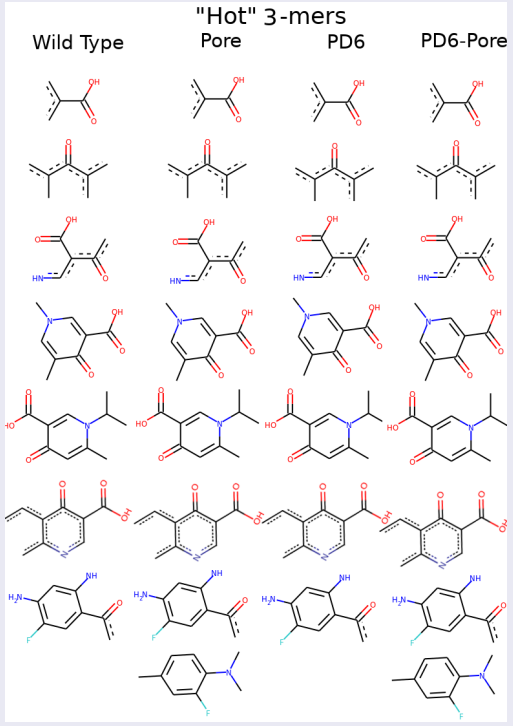
2-mers



2-mers,cont

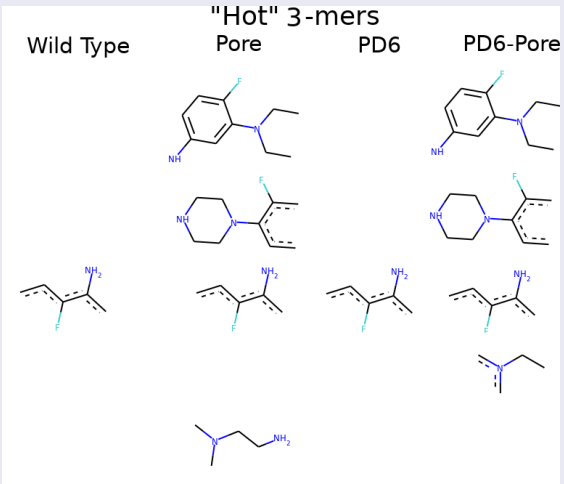


3-mers

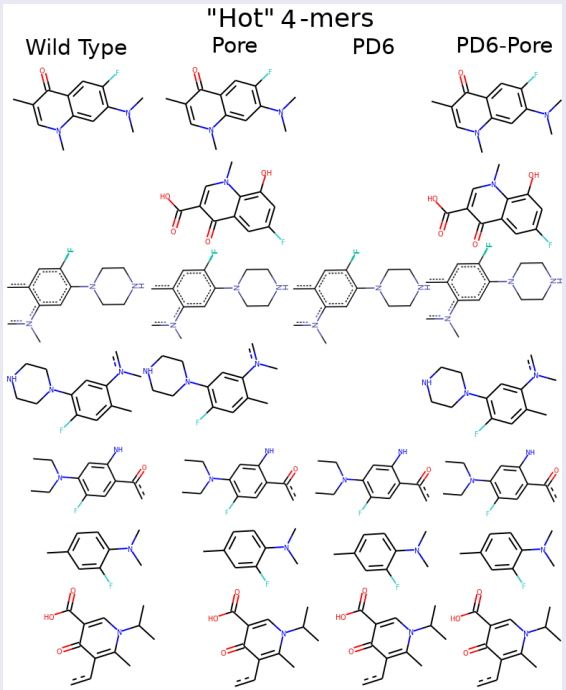


Important *k*-mer molecular fragments from MICs

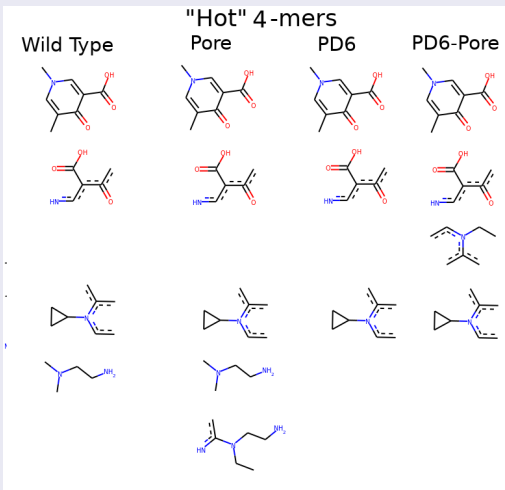
3-mers,cont



4-mers

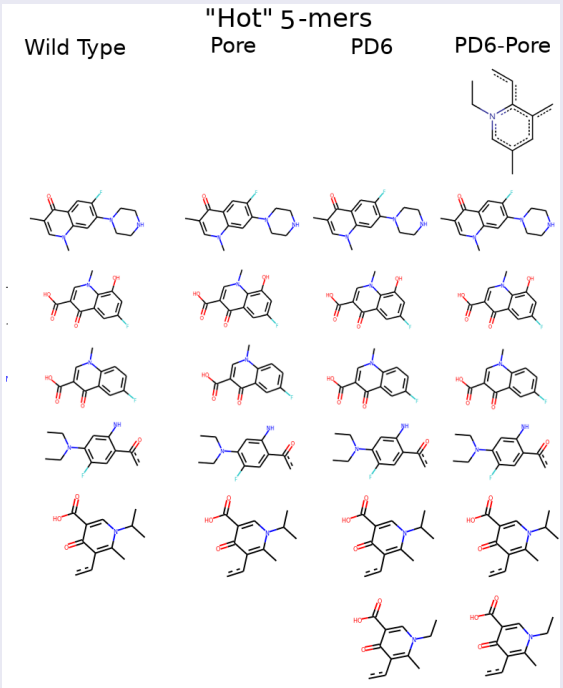


4-mers, cont

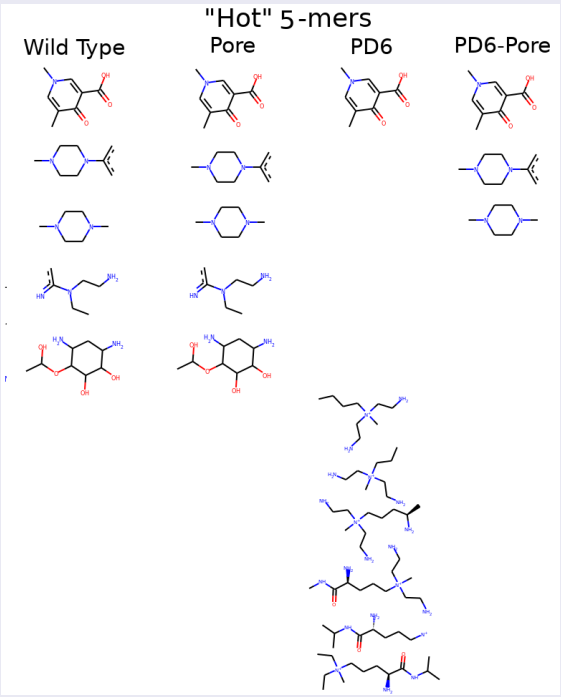


Important *k*-mer molecular fragments from MICs

5-mers



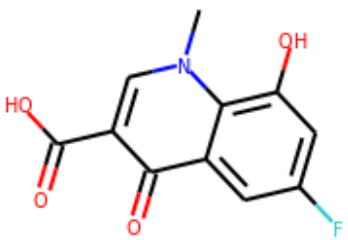
5-mers, cont



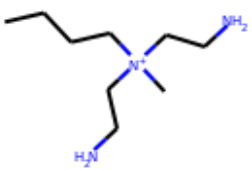
- Important to pore but not WT: Does not get pumped out but may not get through the barrier
- Important to PΔ6 but not WT: Permeates barrier and inhibits growth, but may get pumped out
- Important to PΔ6-Pore but not WT: Inhibits but trouble getting/staying in
- Important to WT and Pore but not others: Likely important to not getting pumped out; may not show up in others because there are fewer barriers

Test CG PMFs for a few interesting fragments?

Pore/PD6-Pore



PD6 Only



- Hypothesis: top fragment is likelier to avoid efflux, bottom is likelier to permeate the outer barrier
- Initial test: coarse-grain and calculate permeation across membrane
- A bit slow because of the requirement to coarse-grain new molecules

Conclusions, Questions, and Future Work

- This is a "vocabulary" directly related to improving minimum inhibitory concentration
- May also carry information about which fragments are related to which aspects of inhibition
- Test CG PMFs for fragments
- Caveat: still relatively small sample size
- Experimental testing? Can we stitch together some purportedly useful fragments?
- Further work: Use descriptors for machine learning as discussed